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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

DECEMBER 1938

ADDRESS OF WELCOME
ELEVENTH ANNUAL GRADUATE FORTNIGHT*

JAMES ALEXANDER MILLER
President, The New York Academy of Medicine

It is a pleasure and a privilege to welcome the participants in this, the Eleventh Graduate Fortnight held under the auspices of The New York Academy of Medicine.

The subject selected this year, "Diseases of the Blood and Blood Forming Organs," is one of unusual interest. It is fascinating in the variety of conditions which it includes, exciting because of the brilliant advances in our knowledge which have occurred in some directions, and yet, also mysterious and baffling because of the unresolved problems which surround the subject.

All this makes the matter one of live interest to all thinking physicians, whether their interest be mainly from the clinical or from the research and theoretical side.

The program which is offered to us is extraordinarily attractive and we are greatly indebted to the Committee in Charge whose unremitting efforts have made such a splendid program possible.

We are, of course, under great obligations to the lecturers who are reporting to us on their scientific and clinical observations, as well as to

* Delivered October 24, 1938.

the clinicians in the hospitals who are offering to us the opportunity to study these clinical problems at first hand.

In addition, the scientific exhibit of this year is of special interest and well deserves careful study.

Altogether it would appear that this symposium is one that it would be difficult to excel.

There is one additional and important factor in the situation which I should like to emphasize, and that is that in this field, as in many others, the basis of the successful treatment of the patient rests upon careful scientific research. The great progress that has been made in this field has been due to the unremitting labor of numerous workers carrying out their investigation under great difficulties. It is, I think, only proper to emphasize the fact that this progress would have been absolutely impossible if it had not been for the use of animals in experimental researches. From the time of Harvey down to the present, advances in our knowledge concerning the blood have been made possible through animal experimentation. This has laid the foundation for scientific knowledge and thus has made possible suitable treatment which has saved many lives.

It perhaps would not be one of the least of the benefits resulting from this symposium if, on the part of the general public as well as of the medical profession, there came a better appreciation of this fact and of the absolute dependence of further medical progress upon continued scientific research through the use of properly controlled animal experimentation.

REMARKS ON THE DIFFERENTIAL DIAGNOSIS AND TREATMENT OF PERNICIOUS ANEMIA*

CYRUS C. STURGIS

SINCE the introduction of the modern methods of treating pernicious anemia, with their strikingly beneficial effects, one need not dwell upon the importance of recognizing the condition at the earliest possible moment. To overlook the diagnosis of a disease for which effective control methods are available, is obviously a regrettable error. In the eighty-nine years since Thomas Addison first described the disease, our diagnostic methods have improved to such an extent that pernicious anemia should be easily recognized in almost every case. In fact, with proper study, it is doubtful if there is any other disease in which the diagnosis can be made during life with a greater degree of accuracy. It is possible to go further and state that the clinician, having the advantage of a therapeutic test and repeated blood examinations during life, can surpass the pathologist in the accuracy of the diagnosis in this disease. This is because there are so many diagnostic features which are present with a great degree of constancy. In general, it may be said that if any person of middle age complains of the symptoms common to all the anemias, such as dyspnea, palpitation, recently developed pallor, weakness and ease of fatigue, and in addition has an achlorhydria, paresthesia of the hands and feet, and recurring attacks of glossitis, the diagnosis is indicated, even before the blood is examined.

After considering carefully the evidences of the disease in approximately 1,000 patients whom we have observed during the past eleven years at the Simpson Memorial Institute, it is clearly apparent that there are at least seven cardinal points of fundamental diagnostic significance. These are usually recognized or eliminated without difficulty; and, if all or even a majority of them are present, then the diagnosis of true Addisonian pernicious anemia is at once established. These are: (1) Achlorhydria; (2) Macrocytosis; (3) High color index; (4) The re-

* From the Thomas Henry Simpson Memorial Institute for Medical Research, University of Michigan. Delivered October 24, 1938, in the Eleventh Annual Graduate Fortnight.

sponse to potent anti-pernicious anemia therapy; (5) Paresthesia; (6) Glossitis; (7) Leukopenia, or the absence of leukocytosis. Each of these will be discussed briefly.

1. *Achlorhydria.* There is no other finding, in any other recognized syndrome which occurs with greater constancy than the absence of "free" hydrochloric acid in the gastric secretions of patients with pernicious anemia. Moreover, all evidence indicates that this condition has always been present in these patients, and that it will invariably remain, regardless of treatment or the disappearance of symptoms referable to the gastrointestinal tract. The presence of hydrochloric acid in the gastric secretion, therefore, should eliminate at once the diagnosis of Addisonian pernicious anemia. In the entire field of clinical medicine there is no diagnostic fact which can be stated with a greater degree of finality. The question will at once be raised regarding those exceedingly rare instances in which it is reported that a patient supposedly had pernicious anemia but did not have an achlorhydria. The answer to this is, first, such an exception is one in many thousands and from a practical standpoint, therefore, it is not of clinical importance. Second, a technical error might well explain the discrepancy. And, third, the patient may have some other cause for the macrocytic anemia, such as sprue, disturbance of the gastrointestinal tract including liver disease, or one of several others. Finally, it should be stated that any conclusion regarding the state of the gastric juice should be based only upon observations made after the injection of histamin, which is the most powerful stimulus to gastric secretion known at present. This is emphasized because a patient may be suspected of having pernicious anemia and an absence of hydrochloric acid has been noted following the use of one of the several test-meals which have been utilized as diagnostic procedures for many years. More than once it has been possible to demonstrate the presence of hydrochloric acid in such patients when histamin has been used as a stimulus to gastric secretion.

2. *Macrocytosis.* All observers are in agreement that when an anemia is present, a macrocytosis is the most characteristic finding in the peripheral blood in patients with this disease. Moreover, this is the first characteristic change to occur when the anemia develops and the last to disappear when the blood approaches normal. By a macrocytosis is meant a mean corpuscular volume which exceeds 96 cubic microns and in some instances may be as great as 140 cubic microns. The actual

volume of the erythrocytes is the most satisfactory evidence of the presence or absence of a macrocytosis although satisfactory information may be obtained from measurement of the diameter of the cells by the Price-Jones technic. By this method it is possible to demonstrate in a macrocytic anemia, that a majority of the cells have a diameter exceeding the average normal measurement of 7.5 microns. It should be appreciated that the level of the erythrocyte count bears some relationship to the degree of macrocytosis. In general it may be said that its degree diminishes as the red blood cell count approaches normal, and that it is more pronounced as the anemia becomes more severe. An exception to this general statement is usually noted when the erythrocyte count falls to a million or less per cubic millimeter. Although the mean corpuscular volume may then be increased, the degree of this change may not be marked, possibly because fragmentation causes the appearance of many small erythrocytes which tend to reduce somewhat the average cell volume.

It is, of course, well known that macrocytic anemias occur which are due to causes other than those responsible for the production of pernicious anemia. Such an anemia may be present in:

1. Certain disorders of the digestive tract, such as gastric resection; "short circuiting" operations on the intestines or intestinal stenosis; liver disease; idiopathic steatorrhea; Dibothriocephalus infestation; and, chronic diarrhea due to various causes.

2. In association with various types of lymphoblastomas such as aleukemic leukemia and Hodgkin's disease.

3. In certain other anemias, as aplastic anemia, chronic hemolytic anemia, anemia of nephritis, anemia of pregnancy, and for a short interval following acute hemorrhage.

4. In myxedema.

5. In sprue and pellagra.

From a consideration of the above numerous causes of a macrocytic type of anemia, it is obvious that the presence of a macrocytosis is certainly not diagnostic of pernicious anemia. On the other hand, if a patient who is suspected of having pernicious anemia, is found to have a microcytic type of anemia, it is *exceedingly strong but not conclusive evidence* against Addisonian pernicious anemia. It should be remembered that a microcytic anemia may occasionally occur in pernicious anemia but in those rare instances when it is present, there is always some complication, the most common being hemorrhage, chronic infection, endocrine dis-

orders, or a dietary deficiency.

3. *Color Index.* What has been said about the macrocytosis in pernicious anemia from a diagnostic standpoint applies almost equally well to the color index which is usually 1.0 or greater. This is because there is a rough parallelism between the height of the color index and the size of the red blood cells. In general, it may be said that when they are largest, the color index is highest; and when they approach normal in size, the color index falls to approximately 1.0. In pernicious anemia during relapse, therefore, a color index of 1.0 or greater is to be expected. It is less than this only: (1) At the beginning of a spontaneous or therapeutically induced remission, when the red blood cells increase at a more rapid rate than the hemoglobin, and the color index, therefore, falls to 1.0 or lower; and (2) In the presence of the same complications which may cause a microcytosis, namely, prolonged bleeding, chronic infection, endocrine disturbances or a dietary deficiency.

4. *Response to Treatment.* The characteristic response to treatment may be considered under two headings: (1) Clinical evidence of improvement and (2) Changes in the blood. They both appear promptly that is, usually between three and six days after therapy is begun. At this time every evidence becomes apparent that the patient's condition is changing for the better. This is indicated by the disappearance of nausea and vomiting; the appetite is greatly improved; if fever is present, the temperature falls to narmal; the patient regains his strength rapidly and, in a relatively short time, is able to be up and about. There are very few conditions encountered in the practice of medicine which show such a remarkable and prompt response to specific therapy.

Indication of improvement in the blood is evidenced, first, by a striking increase in the number of reticulocytes, which begins between the third and sixth days after treatment, reaches the highest peak between the seventh to ninth days, and returns to normal at about the end of two weeks. With this change, the total erythrocyte count increases at about the rate of 200,000 to 400,000 red blood cells a week, depending upon the initial level of the erythrocyte count, the potency of the antipernicious anemia therapy, and the presence or absence of certain complications, such as infection. When these two characteristic responses occur it does not necessarily mean that the patient has pernicious anemia but it does indicate that either the disease is present or that the patient has a pernicious anemia-like blood condition which is seen in association with

certain disorders of the digestive tract, including liver disease, or the macrocytic anemia of pregnancy, Dibothriocephalus latus infestation, sprue and possibly pellagra.

The absence of such a response is clear-cut and almost conclusive evidence against the diagnosis of pernicious anemia, provided the red blood cell count is below three million and a liver extract of known potency has been administered parenterally in appropriate doses. It is true that the hematological response may be less in patients who have an acute infection or extensive arteriosclerotic changes, but it is never, under any circumstances, completely lacking.

5. *Paresthesia.* One of the most constant subjective evidences of this disease is the presence of numbness and tingling of all four extremities. In most textbooks it is stated that this complaint is present in about 80 per cent of these patients, but if specific information is obtained concerning this symptom, it will be found to be present in 90 per cent of the cases. It is encountered in patients who have involvement of the nervous system due to other causes, but in these conditions it is not so common to have it involve both the hands and the feet, as it almost uniformly does in pernicious anemia. The absence of this symptom does not eliminate the disease as a diagnostic possibility but indicates that a careful search should be made for some other explanation of the patient's condition.

6. *Glossitis.* Careful questioning of patients with pernicious anemia will reveal that about two-thirds of them give a history of having had attacks of glossitis, characterized by periodic recurrences of painful, sore tongue. The patients usually state that the condition almost invariably has remissions and exacerbations. The term "recurrent glossitis" is, therefore, appropriate. In addition, 42 per cent of our group had definite and easily recognizable atrophy of the papillae of the dorsum of the tongue, about which there could be no doubt. It is interesting to note that a patient's tongue may appear perfectly normal despite a history of severe recurrent glossitis and, on the other hand, there may be obvious atrophic changes without a previous history of symptoms referable to the tongue. Another observation in our experience has been that never has a patient with pernicious anemia been observed with an abnormally coated tongue when an anemia is present, regardless of the intensity of the symptoms. In general, it may be said that the existence of a coated tongue in a patient suspected of having pernicious anemia, casts considerable doubt upon the diagnosis.

Neither a history of glossitis nor atrophy of the tongue are conditions which are commonly encountered in clinical medicine and when present they should always suggest the possibility that the patient has pernicious anemia. It should be kept in mind, however, that similar tongue symptoms may occur in other conditions, such as sprue, pellagra, achlorhydric-microcytic anemia and various intestinal disorders.

7. *Leukopenia, or the Absence of Leukocytosis.* A diminished number of leukocytes is almost always observed in patients with pernicious anemia who have an anemia and are in a condition of relapse. This is true even in the presence of a severe pyogenic infection which ordinarily would evoke a leukocytic response. There is a tendency for the leukocytes, however, to increase in number at the beginning of a remission, either spontaneous or therapeutically induced. Moreover, it is a well known fact that if an infection occurs at that time, there may be an exaggerated response as indicated by a striking rise in the leukocytes to a level of 30,000 or 40,000 or greater. A leukopenia then is the rule during relapse. A leukocytosis which has been reported during this stage may well be an erroneous observation, which can be accounted for by the enumeration of nucleated erythrocytes in the counting chamber as leukocytes.

Splenomegaly

The older observers state that the spleen is palpable in perhaps 20 to 40 per cent of the cases. If this was the situation then, it is not true now, for it is rare to observe a spleen which is enlarged to a point where it is palpable beneath the left costal margin. Furthermore, the presence of a grossly enlarged spleen is strongly suggestive evidence that the patient has some cause other than pernicious anemia for the anemia. This is most frequently one of the lymphoblastoma group, such as aleukemic leukemia or Hodgkin's disease. Widespread liver disease, such as cirrhosis, may be associated with a macrocytic anemia and a moderately enlarged spleen. The anemia may be accounted for on the basis that there is inadequate storage of the erythrocyte maturing factor in the organ, and the splenic enlargement has been regarded as due to chronic congestion.

Remarks on the Treatment of Pernicious Anemia

Twelve years have now passed since the modern treatment of pernicious anemia was introduced by Minot and Murphy. During that

interval, ample opportunity has been afforded numerous observers to study the effects of various types of treatment and compare their results with those noted before the existence of specific therapy. Prior to 1926, the status of the treatment of pernicious anemia is well expressed in the following quotation from a monograph on pernicious anemia published by Dr. Frank Evans, just a few months before the liver treatment was introduced. He states: "The treatment of pernicious anemia is discouraging. No patient with true pernicious anemia has ever been cured. However successful any therapeutic procedure may have been at first, there comes a time when the patient does not react to any treatment, he gradually grows worse, and death ensues. Furthermore, no treatment has so far been suggested which can be shown to have prolonged life."

The conclusions regarding treatment which are expressed in this article, are based upon the observation of approximately 1,000 patients who have been treated by various methods of liver and stomach therapy between the years 1927 and 1938. They have been observed, at intervals, for periods varying between a few months and eleven years.

Of this group, approximately 10 per cent, or 100 patients, are dead. The fatal cases can be divided into two main groups of equal importance numerically: First, those who died of complications incident to extensive involvement of the nervous system; and, second, those who died of incidental and unrelated diseases. The first group still remains a challenge to the methods of treatment of pernicious anemia and calls for an improvement especially in the management of the spinal cord lesions. The second has no direct association with pernicious anemia but is concerned with the prevention and treatment of unrelated diseases, chiefly degenerative, which are a common cause of death of persons who belong to the middle age or elderly group. None of the patients in either group as far as could be determined, died of anemia *per se*.

The Effect of Treatment on Spinal Cord Lesions

Whereas one-half of the patients who died, did so as a result of complications incident to spinal cord changes, a very large proportion of these, either presented themselves for treatment for the first time when the neurological manifestations were advanced, or failed to follow instructions regarding treatment, and, as a result, the anemia failed to improve or there was a hematological relapse. Furthermore, many of them were treated before the more effective parenteral methods of administering

liver extract were in widespread use. It is conceivable that had these been used, better results would have been attained. A typical example of a patient for whom the most efficient therapy may accomplish very little, is as follows: One who when first seen, has an ataxic, spastic paraplegia, and is either confined to bed or has a great deal of difficulty in locomotion. Frequently the anemia is not severe as the red blood cell count may be in the vicinity of 3.5 million per cubic millimeter and the hemoglobin approximately 70 per cent. If there is not already a failure of function of the sphincter of the bladder when the patient is first observed, this eventually appears and results in a distension of the bladder with the development of a residual urine which almost always becomes infected. When this occurs, regardless of intensive therapy, it is exceedingly difficult to cause the blood to return entirely to normal limits, although it may improve considerably. There are two views concerning this partial failure of treatment. One is that any infection may inhibit the effectiveness of the antipernicious anemia therapy in some obscure way. The other is that such a patient may have two independent causes for the anemia, each of which contributes simultaneously to the observed level of the erythrocytes and hemoglobin. One cause is the usual mechanism which is believed to account for the anemia of pernicious anemia. As would be expected, this responds to liver or stomach therapy as indicated by a reticulocyte rise and some increase in the hemoglobin or red blood cells. The blood, although improved, does not return entirely to normal, because a second cause, namely chronic infection, continues to act regardless of the use of specific therapy. As long as the infection is present, therefore, the anemia will persist. Both considerations are hypothetical ones which explain the facts adequately, but the latter one appears to be more plausible.

Consideration of our present methods of treatment indicates the hope that the best results in the management of the nervous manifestations lie in the prevention of the degenerative changes, rather than anticipating that they can be improved or eradicated after they have once been established. Furthermore, it seems rational to speculate that if future investigation is to yield a helpful form of treatment, it will most likely be the result of research in the field of vitamin or closely allied therapy. It is not difficult to anticipate that in the near future, a specific deficiency will be found which accounts for the changes in the nervous system. Even if this be recognized, it must be admitted that it is hardly justifiable to assume

that a correction of such a deficiency will cause regeneration of the tracts in the spinal cord and hence restoration of function.

For the present, it may be said that there is a reasonable certainty of preventing the development or progression of spinal cord changes, if the red blood cells can be brought to a high normal level and maintained there constantly. Even this statement can be challenged as lacking in absolute scientific proof, but it must be conceded that it is more than just a fair assumption. We have never observed objective signs of cord changes develop or progress during a period when the blood has been uniformly normal. Having this knowledge, the intensive treatment of the anemia is certainly the obvious and logical principle upon which our treatment should be based.

The second and equally large group of fatalities requires only brief comment. These patients succumbed to the common causes of death in this age group, which goes to prove that our life expectancy tables are correct. Disregarding the fact that a patient of fifty may have pernicious anemia, the life expectancy for a healthy person of that age is only a limited number of years. It is to be anticipated that among a group of persons between forty-five and sixty-five years, some will develop hypertension, malignancy, arteriosclerosis, nephritis, pneumonia and other diseases, and encounter accidents which will prove fatal. This is precisely what occurred in our group of patients, and there was not the slightest evidence to indicate that there was anything but a coincidental association between the two disease conditions.

In conclusion, let me make several remarks about the treatment of pernicious anemia in general. Although the Committee on Standardization of Antipernicious Anemia Medication has done most creditable work, they would be the first to admit that the task is beset with difficulties. The chief one is that the units, as assigned to the products of different manufacturers, are not always interchangeable. For example, one product may contain fifteen units per cc. and another, one unit per 2 cc. yet if equal unit doses are given, the clinical results are not always the same. At present, therefore, the advice of the manufacturer should be followed and the result checked by frequent determinations of the red blood cell count. After all, the important thing is to give an adequate amount of the antipernicious anemia principle; there is no recognizable deleterious effect known to result from an excess of it.

It appears to be generally agreed that the most satisfactory treatment

of the disease at present is the intramuscular administration of liver extract. This has the advantage of eliminating all question of absorption from the gastrointestinal tract; the blood can be maintained at a normal level by an injection given at intervals of one to three weeks; and this form of treatment will be successful in patients in whom the oral method fails.

There is a possible, but unproven, danger that in using the highly refined products, some substances may be eliminated which are beneficial to the patient. Crude liver extract is known to contain the entire vitamin B complex and it is considered that this substance is related to the pathologic changes in the spinal cord. There are, however, no data which indicate that the addition of vitamin B influences favorably either the blood or changes in the nervous system.

THE NEUTROPENIC DISEASES*

ROY R. KRACKE

THE estimation of the white blood cells has been done now for over fifty years but up until just a few years ago a decrease in the number of leukocytes was regarded only as a diagnostic sign. However, within the past fifteen years neutropenic states have assumed more and more importance not only because of the appearance of new diseases characterized by neutropenia but also because it has become generally recognized that when the white blood cells fall to a low level the patient occupies a precarious position because neutropenia means increased susceptibility to bacterial invasion. It is quite possible that the degree of susceptibility to infection may in some instances be inversely proportional to the number of circulating neutrophils. Furthermore, this lends renewed emphasis to the work of Metchnikoff, who nearly fifty years ago emphasized the predominant role of circulating blood cells in combating bacterial invasion. Since his time the pendulum of emphasis has swung toward the role of immune bodies rather than the cellular theory of body defense. If careful study of the neutropenic diseases serves to re-emphasize the importance of cellular body defense, it will indeed be worthwhile.

Up until recent years the various leukopenic states were usually called "secondary" because they were known to accompany some other disease process. We are quite familiar, of course, with the numerous diseases that are stated to be characterized by neutropenia. These include such common ones as measles, German measles, mumps, respiratory influenza, malaria in its chronic form, the recently recognized Brucellosis, typhus fever, early typhoid fever, and even overwhelming infectious processes produced by pyogenic organisms. Furthermore, a neutropenia is often seen in such conditions as Banti's disease, some of the lymphogranulomata, Hodgkin's disease occasionally, glandular tuberculosis, and in many conditions in which the bone marrow is directly involved, such as multiple myelomata, miliary tuberculosis and bone marrow carcinomatosis.

It is frequently stated in textbooks that such secondary neutropenic

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syndromes are brought about by the action of bacteria or their toxins. This seems to be an unsatisfactory explanation for I know of no scientific evidence that proves that certain bacterial toxins may depress leukopoietic function, unless it be the work of Dennis,[1] who placed collodion capsules containing growing bacteria in the peritoneal cavities of rabbits and observed the leukocyte depression that followed the absorption of the bacterial toxins from the capsules. In some of the infectious diseases, no doubt, neutropenic disorders occur because the available circulating leukocytes are speedily drawn to the source of infection in an effort to combat it and this would explain this type of neutropenia more satisfactorily than to assume a toxic effect of bacterial toxins on marrow activity.

Many of the infectious diseases are characterized by severe types of neutropenia in occasional instances. I have observed a young university student who was admitted to the hospital with a leukocyte count of 800 with 10 per cent neutrophils and who was given a tentative diagnosis of agranulocytosis, yet who four days later developed the typical rash and clinical findings of typhus fever with a speedy return of the leukocytes to normal. Only recently I studied a young girl who for four days had suffered from profuse watery diarrhea with severe abdominal cramps and high fever and who on admission to the hospital showed a leukocyte count of 700 with 6 per cent neutrophils. A tentative diagnosis of agranulocytosis was made but bacterial examination of the stools revealed practically a total absence of the normal bacterial flora and practically a pure culture of Bacillus paratyphosus B was obtained. After recovery her leukocyte count returned to the normal level. Here was an instance then of food poisoning by this organism accompanied by an extremely severe neutropenia which lasted for several days. I should point out that this patient was particularly fortunate that during this time she suffered from no further bacterial invasion of the tissues. These examples illustrate the extremely low level to which the leukocytes may fall in response to certain types of infectious diseases. In such instances how can one explain the mechanism of leukopoietic depression? Is it because the bone marrow was overwhelmed by bacterial toxins or were the leukocytes drawn to the area of infection as fast as they were produced? I do not believe that the answer to this question can be stated at this time.

In addition to the infectious diseases that are accompanied by leukopenic disorders, there are other agents capable of producing this syndrome. Among these is benzene (C_6H_6) which when injected into

laboratory animals practically invariably produces severe leukopenia within three to four days. Also if benzene is given to animals or to the human by mouth, chronic leukopenic disorders will usually result. It has not been many years since this product was used in therapeutics to reduce the white cell count in cases of chronic myelogenous leukemia. For many years in our laboratories at Emory University we have attempted to determine the mode of action of benzene on the leukopoietic centers and we are impressed with the concept that benzene does not reach the bone marrow as such but that it undergoes chemical transformation before action on the marrow, although I am unable to state its exact chemical state when it reaches the marrow cells. Benzene does not confine its action to the leukopoietic centers, particularly if given in large doses, but involves erythropoiesis and thrombopoiesis as well. Many animals poisoned with benzene show the hematologic picture of complete marrow aplasia just as does the human being who may develop aplastic anemia if unduly exposed to this agent. There are other chemical agents known to be capable of depressing the leukocyte count in an occasional individual. These include arsenic occasionally in its inorganic form and gold salts, some of which do not contain the benzene ring. Even gasoline fumes according to Alice Hamilton[2] may cause a depression of leukocytes and there are probably others closely related to benzene that have not yet been emphasized in medical literature.

The effect of excessive radiation on the bone marrow has long been known to be characterized by leukopenic disorders as was so well demonstrated by the famous instances of aplastic anemia following exposure to gamma rays in the incidence of poisoning among the luminous clock dial painters[3]. Also severe leukopenia has been reported from the drinking of so-called "radio-active water" and among a few individuals who have worked with radium. It has been reported in a sufficient number to clearly indicate that leukopenic disorders can arise from it. Even Roentgen rays have been reported in numerous instances to have produced severe leukopenic states.

I feel that I should point out again, as I have previously, that there seems to be some danger of the development of leukopenia in an occasional person who has been subjected to excessive radiation from sunlight. I have studied the blood of many people on their way to and from Florida where sunlight seems to be the chief object of the journey and I can not escape the impression that leukocyte counts are lower after

excessive exposure to the rays of the sun.

It is well established now that a deficient diet may be responsible for leukopenia. This has been shown by Langston and Day[4] at the University of Arkansas, who have been able to produce consistently chronic leukopenia, erythropenia and thrombocytopenia in monkeys after feeding them with a diet deficient in vitamin G. Furthermore, Miller and Rhoads[5] have produced similar evidence that a black-tongue producing diet in dogs may be accompanied by leukopenia and stomatitis. Therefore, in the treatment of the neutropenic diseases it would be well to consider carefully the diet of the patient and to provide one that is not lacking in any of the essential vitamins.

It has been long recognized that marked leukopenic states may accompany disease involving the adrenal cortex and in particular it is a consistent finding in Addison's disease which is characterized by weakness, fatigue, marked hypotension, occasionally pigmentation of the skin, and nearly always severe leukopenia. As to whether or not this leukopenia is brought about by deficiency of the adrenal cortical hormone is open to question. Britton and Corey[6], at the University of Virginia, have commented upon the marked leukopenia found in their adrenalectomized cats.

It would be well at this point to discuss another large group of agents that are now definitely recognized to be capable of producing the most severe neutropenic states. I refer to the various pain relieving drugs that have attracted so much attention in recent years. It has now been seven years since I first pointed out that certain pain relieving drugs may cause the disease, agranulocytosis. The first intimation to us that this could be possible was the admission of a patient to the Emory University Hospital in 1930. This patient was a middle-aged woman who had been ill with so-called influenza for several weeks and who during that time had been given a considerable number of analgesic agents, including amidopyrine, phenacetine and acetanilid. This patient was brought to the hospital because of her peculiar blue color which was soon determined to be due to methemoglobinemia. It was apparent, of course, that the methemoglobinemia in this instance was caused by prolonged administration of acetanilid. Much to our surprise we discovered also that this patient had agranulocytosis. The association of these two findings led us to our first realization that these drugs may be responsible for the leukocyte depression. I shall not burden you with a recital of the development and final proof of this concept but shall merely point out that a study of the cases

of agranulocytosis that we had seen up to that time, on careful questioning of the relatives of the deceased patients, added evidence to the effect that all of them had taken such drugs prior to their illness. These findings, coupled with statistical studies which showed that people who developed agranulocytosis were the largest drug users and that the geographic incidence of the disease corresponded to countries where those drugs were in wide use, added further support to the concept. For two years then we attempted to produce the disease in laboratory animals by the feeding and injection of such preparations as amidopyrine, pyramidon, acetanilid, phenacetine and proprietary mixtures of these, but were not able to do so. The final proof of the correctness of this concept has come from two lines of research. One of these, and the most conclusive, has been the occasional experimentation that has been carried out in which patients who have recovered from agranulocytosis have been given as little as a single dose of amidopyrine and the disease reproduced in them. This type of experiment has been carried out by Madison and Squier[7], and subsequently by others throughout the world and has produced in my opinion ample confirmation that an occasional individual is so sensitive to the action of these drugs that the bone marrow may suddenly be thrown into a non-productive state by the ingestion of as little as a single therapeutic dose.

The second confirmation of this concept has come from Denmark where Plum[8], in his most exhaustive monograph on this subject, has shown that up until 1934, there were over one hundred cases of agranulocytosis in that country and that the increasing incidence of the disease up to that time exactly paralleled the consumption of amidopyrine which in that country is imported, and that when the use of amidopyrine was forbidden by Government decree the disease at once completely disappeared. So today in Denmark, because of careful restriction in the use of this drug, the entire question of agranulocytosis has apparently been completely settled.

In addition to amidopyrine certain other drugs will produce marked leukopenic disorders. These include the organic arsenical compounds as well illustrated by the numerous instances of agranulocytosis and aplastic anemia that have followed the injection of as little as one dose. It has long been recognized that arsphenamine in an occasional person may produce aplastic anemia and I believe that it should be emphasized that this type of drug can also produce a hematological syndrome that is actually

agranulocytosis in which the marrow depression is limited exclusively to depression of the granulocytes. This is well illustrated by the recent report of Blew,[9] from the United States Navy, who observed agranulocytosis in three young sailors, one of whom had received sixty-eight injections of neoarsphenamine; another having received a large number and a third having received only three injections. In these patients the red cell pictures were not affected. Such observations, coupled with many others in the literature, indicate very clearly that the organic arsenicals can produce agranulocytosis as well as aplastic anemia. Furthermore, I have observed a colored boy who developed this disease after one injection of neoarsphenamine. It is well established now that the administration of dinitrophenol can produce marked leukopenia since several instances have been reported. Since dinitrophenol, however, produces cataracts in an occasional person as well as agranulocytosis, it is today no longer a serious problem in this respect. I do not believe that well informed doctors use dinitrophenol any longer.

The drug causation of neutropenic diseases has received and should receive renewed emphasis at this time since the introduction of sulfanilamide. I am able to find records now of fourteen instances of agranulocytosis following the administration of sulfanilamide. In these fourteen, which have been reported from widely scattered areas, in every instance the dosage of the drug has been quite large and in most of them has extended over a period of several days to several weeks. I am unable to find a record of the disease having followed small quantities of this preparation, such, for example, as one or two doses, and in this respect this type of leukopoietic depression seems to differ from that produced by amidopyrine. Furthermore, it should be pointed out that sulfanilamide in an occasional patient produces neutropenia of a mild to moderate degree and not to the point of complete agranulocytosis. I had observed patients with leukocyte counts around two, three or four thousand cells, the reduction in the cells being at the expense of the neutrophils. Such patients usually recover from the depressing effect of the drug unless the count has fallen so low that they have become invaded by pathogenic bacteria in which event, of course, death may be brought about by the overwhelming sepsis just as in other cases of agranulocytosis. I have been particularly concerned recently in the effect of sulfanilamide on the blood and have observed now several instances in which this preparation is capable of producing a marked stimulation of the leukopoietic centers

resulting, therefore, in extremely high leukocyte counts and I note that this observation is recorded fairly frequently in the medical literature. I have observed leukocyte counts over one hundred thousand per c.mm. during the course of treatment with sulfanilamide and it is not unusual to see leukocyte counts of thirty, forty or fifty thousand cells per c.mm. of blood. I am unable to explain why sulfanilamide in an occasional person will depress leukopoiesis and in another person apparently stimulate leukopoiesis. Of course, this drug is also capable of producing in an occasional person marked degrees of hemolytic anemia and in these instances, a high degree of leukopoietic activity usually accompanies the regeneration of red cells. The fact that sulfanilamide itself produces leukocytosis in an occasional person, often has an important practical bearing on the treatment of the patient in question. For example, I have observed a young woman who developed streptococcic puerperal sepsis and was treated intensively with sulfanilamide for six days. At that time her leukocyte count was sixty thousand per c.mm. and at the same time she had shown such marked improvement that it appeared clinically that the infection had been overcome. The question that presented itself then was—What was the cause of the leukocytosis? If it were caused by sulfanilamide then there was no cause for alarm but, on the other hand, if it meant that the infectious process was still rampant, then further therapy with sulfanilamide was clearly indicated. I have observed this same problem now in several such instances and it presents the question as to when the drug should be discontinued.

Finally, in concluding this discussion of drugs, it must be pointed out that amidopyrine has been combined with so many other preparations and the resulting compounds sold under such a wide variety of names, that it is practically impossible for the physician to know whether or not the average pain-relieving preparation contains the drug. In recent publications I have shown a large number of preparations that contain this particular drug, so I will not repeat it here. The fact that amidopyrine has been so widely used is a testimonial to its therapeutic efficacy in the relief of pain and, of course, it is widely recognized as a valuable agent for that purpose. However, if the physician chooses to use amidopyrine, he should do so knowingly and should write a prescription for it. In view of the dangers of this drug, I can see little excuse for physicians prescribing various compounds manufactured by different drug firms which may or may not indicate the presence of the drug. I am well aware of the fact

that the desk of the average physician is daily cluttered up with literature and samples from various drug firms extolling the virtues of their various preparations, so much so that the average doctor nowadays is lost in a maze of commercial pharmacology. It appears to me that the science of pharmacology among doctors is a lost art. If one chooses to use amidopyrine and other similar compounds it should be done by prescription and we should not depend for pharmacological knowledge on the literature of drug manufacturers or upon the exhortations of detail men. The new food and drug law which will become effective shortly offers some measure of protection to the public against the consumption of such preparations unknowingly since it requires the formula of patented compounds to be printed on the package. It will be possible, therefore, for that part of the public that is informed on this question to read the label and see whether or not a patented compound contains dangerous drugs.

Since it is now obvious that leukopenic disorders can be caused by such a wide variety of physical agents, chemical compounds, drugs, dietary deficiencies and hormone disorders, it is incumbent upon the physician when confronted with a patient with leukopenia to make careful search for possible causative factors, in order that the cause may be removed. This may prove to be the most important part of the treatment.

I shall now discuss briefly those diseases of the blood that are characterized by neutropenia. According to modern classifications these are three in number as follows: agranulocytosis, aplastic anemia, and aleukemic leukemia. In view of the previous discussion of the factors that are capable of depressing the leukocytes of the blood, it is unnecessary to consider further the etiology of agranulocytosis except to state that the evidence seems quite adequate that the great majority of these cases are caused by the ingestion of some of the drugs mentioned before and notably amidopyrine.

I am quite ready to admit, however, that all cases of agranulocytosis are not caused by ingestion of drugs. There is some evidence to indicate that the disease may arise from an infectious origin, or for that matter from a filterable virus. In this connection there is a recent report of considerable interest from Lawrence and Syverton[10]. These workers discovered an instance of spontaneous agranulocytosis in a cat and were able apparently to transmit the disease through ten series of cats by the injection of the agranulocytic livers of the preceding animals. They concluded

that there is in the cat a transmissible disease which seems to be caused by a filterable virus which is characterized by severe neutropenia.

Within the past three years there has been apparently a reduction in the number of cases of agranulocytosis but with the increasing use of sulfanilamide I am of the opinion that a new wave of the disease may make its appearance.

The chief diagnostic finding in agranulocytosis is the extreme leukopenia. The cellular reduction, however, is not confined to the neutrophils but involves the other blood cells as well. Therefore, a more correct designation of the condition would probably be, malignant leukopenia. The method by which the offending agent depresses the marrow function is not known. It is probable that the marrow depression antedates the leukocytic depression in the peripheral blood. I have had opportunity to study one patient with daily blood studies before the leukocyte depression became obvious in the blood stream and also of studying the same patient for four days before clinical evidence of the disease became apparent. It seems that the condition develops first by a cessation of cellular output from the marrow; this in turn causing a slow decrease of the leukocytes of the blood and then the neutrophils may be entirely absent for several days before clinical symptoms appear. The clinical symptoms in most instances result from bacterial invasion. Therefore, when the patient is first seen the disease is usually in what may be termed "the terminal stage of the process". Most patients when first seen have already become the victims of varying types of bacterial invasion and may present varying degrees of ulceration of the soft tissues of the oral cavity or about the anus or vagina and in some instances blood stream invasion may have already taken place. There has been some question concerning the pathology in the bone marrow and in former years it was believed that the marrow becomes aplastic in its cellular content with an actual quantitative decrease in the leukopoietic centers. However, Fitz-Hugh and Krumbhaar[11] have pointed out that in many cases the marrow was actually hyperplastic and in my experience this has proved to be true. There seems to be an arrest of development of the neutrophils in the marrow, this usually taking place at the myeloblastic level so that actually the marrow may be crowded with young, immature leukoblasts and in this respect the pathology of the marrow does not differ from that often times seen in the marrow of a patient with aleukemic leukemia. Furthermore, as Rhoads has demonstrated, even in aplastic anemia in

which the peripheral blood has become markedly depleted of all cell types, the marrow in those patients may also show such a hyperplasia. This gives rise to the possibility that common etiological factors may be operative in some of these diseases, producing varying types of hematologic pictures in the peripheral blood, and a variety of clinical syndromes.

The patient with agranulocytosis seldom shows any disturbance of the red cells and hemoglobin unless the process should happen to become prolonged. Furthermore, the platelets in the blood are usually not disturbed. I should like to point out, however, that there is no reason why a patient with agranulocytosis should not be anemic and indeed many of them are anemic because a considerable proportion of them have been suffering with other diseases beforehand.

In my opinion the presence of clinical hemorrhage does not rule out agranulocytosis. I have studied typical instances of this disease which at autopsy showed varying degrees of hemorrhage, usually in the form of petechial spots. This, however, is not the usual finding. The patient with this disease obviously will present a variety of clinical symptoms, depending not only upon the extent of reduction of the white cells, but also upon the degree of bacterial invasion. Ulcers of the soft tissues in areas normally inhabited by bacteria are common. There is usually a definite febrile course and in many patients there is marked edema of the soft tissues about the mouth and the neck. This predominant edema which occurs so often seems to be an attempt at a cellular response to invasion of organisms; but since cells are not available for this, the inflammatory response is mainly one of fluid into the tissues.

In many instances patients with agranulocytosis exhibit a degree of prostration which seems entirely out of proportion to the physical findings. I have studied patients who showed a completely negative physical examination and in whom no external lesions of any sort could be found, yet the same patients presented a high fever, were partially comatose, were sometimes irrational and delirious. Even at autopsy it was extremely difficult to find gross pathologic changes that could account for such severe clinical manifestations.

The treatment of agranulocytosis still remains highly unsatisfactory in spite of the many efforts made and new preparations introduced to combat it. It would require a long recitation for me to enumerate the therapeutic agents that have been used in this disease; suffice it to say that these have now centered around the use of repeated blood trans-

fusions, liver extract by injection in large amounts, pentnucleotide or other nucleic acid products by injection, and yellow bone marrow given by mouth. There seems to be little benefit from the use of radiation. I am convinced that if there should be a choice between agents used to stimulate a renewed marrow output, liver extract would be much preferable to pentnucleotide. Our experience with pentnucleotide has been quite disappointing, but here I should point out that no one man probably has treated a sufficient number of cases to form a proper evaluation of therapeutic agents. After all, in this disease do we not expect too much of any therapeutic agent, especially in view of the considerations that I have brought out before, that is, not only is the patient depleted of granulocytes, but in addition to this, often times has become overwhelmed with invading organisms, so that there are two serious and distinct diseases to treat, either of which promises to be fatal. It is indeed expecting the impossible of a therapeutic agent that it be able not only to stimulate renewed output of leukocytes but also to successfully combat overwhelming infection.

Although the use of yellow bone marrow by mouth has been recommended, I do not believe that adequate evidence as yet has been presented to prove its therapeutic efficacy. Agranulocytosis, however, is an emergency illness and the use of any therapeutic agent is justifiable if it offers any promise whatever. Therefore, it is my practice to recommend the use of all of these things I have just enumerated; that is, blood transfusions repeatedly, liver extract in ten times the ordinary dosage by injection, pentnucleotide, yellow bone marrow by mouth and symptomatic therapy; but even with all of these, the mortality rate in our more recent series of cases very closely approximates that of the earlier years.

In this paper I shall not attempt to discuss aplastic anemia since this question has been adequately presented by Dr. Rhoads, except to point out that I know of no therapeutic agent that has proved to be of any success in the treatment of this disease, particularly the so-called "idiopathic" type. I have observed patients with hematological aplastic anemia following arsphenamine therapy who usually recovered with cessation of the injections of the drug and the use of transfusions.

The other disease of the blood characterized in many instances by severe leukopenia is that known as aleukemic leukemia. This disease is unquestionably a part of the general leukemic process. It is characterized by hematological findings that in some instances are extremely difficult

to evaluate. The patient usually shows a reduction in the number of red cells depending upon the severity and duration of the process, and in my experience the red cell picture is usually a macrocytic type of anemia. The patient also may present varying hemorrhagic disorders because of a reduction in the number of blood platelets. If they are below fifty or sixty thousand per c.mm., hemorrhages may supervene at any time.

A characteristic feature in nearly all of these cases is a moderate to severe reduction in the total number of leukocytes. The cells may range from the normal figure, or slightly above, down to only a few hundred cells per c.mm. and the lower the cell count, the more precarious becomes the status of the patient. Furthermore, the same patient may show a great variation in the number of leukocytes at different times. I have observed a child with a leukocyte count of four hundred cells per c.mm. and nearly all of these cells were myeloblasts. Six days later this same patient had a total leukocyte count of one hundred and sixty thousand per c.mm. with death shortly afterwards. This merely illustrates the extreme variations in the total number of leukocytes that may be seen in what appears to be aleukemic leukemia. However, many of the more chronic forms may extend for months and perhaps years with an extremely low leukocyte count, only two, three or four thousand, with the percentage of granulocytes quite low. Finally such patients may die because of intervening infectious processes or the count may suddenly become elevated so that what was formerly a chronic type of aleukemic leukemia suddenly changes to an acute form usually of the myeloblastic type with an early termination.

Naegeli stated that the patient with aleukemic leukemia usually lives longer than those patients with high cell counts. Assuming that both are chronic in type, this has not been my experience. The chronic form of aleukemic leukemia does not have, in my experience, the life expectancy of the patient with chronic myelogenous leukemia with high cell counts.

The physical findings in these patients are quite variable; some may show splenomegaly and others not show this finding. Many of them have complications of hemorrhagic disorders; most of them show variable degrees of anemia; some show intercurrent episodes of infection. The treatment seems entirely unsatisfactory. A multitude of therapeutic agents have been employed. Blood transfusions, of course, remain the bulwark continually to restore depleted red cells and perhaps leukocytes. All types of hematologic agents have been employed with no success. Radiation is

usually employed, sometimes directed toward the spleen, if there is splenomegaly, and occasionally as a spray over the bony structure. I do not believe that there is evidence to indicate that these patients are materially benefited even by radiation. Whether or not their life is prolonged by its use, I am unable to state. I do know that we lose these patients invariably after varying periods of time.

Finally I would like to mention a rather obscure leukopenic syndrome that has repeatedly come to my attention, one I have termed "chronic neutropenia", which may have its origin from any of the causes I have enumerated before. This is occasionally seen in the half-well and half-sick patient who often times haunts the doctor's office. Such a patient may show a leukocyte count of only two to three thousand, this being at the expense of the neutrophils. They seem unusually susceptible to excessive fatigue, easy tiring and increased susceptibility to infection. Such patients may present this syndrome over a long period of time and in some of them the use of liver extract by injection has proved to be a valuable agent, whereas in others the correction of dietary deficiencies seems to be the proper treatment.

In conclusion, I desire to emphasize the multiplicity of factors that apparently are conducive to the neutropenic state and the necessity for careful investigation relative to these factors in every patient who presents this syndrome. Especially is this important in view of the inadequacy of our present therapeutic agents. I believe that we can do much more for the neutropenic syndromes by working toward their prevention than by correction after they have once developed.

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RECENT ADVANCES IN KNOWLEDGE OF SOME OF THE COMMON DISEASES OF CHILDHOOD*

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RECENT advances in medical knowledge have modified the diagnosis and treatment of so many of the common diseases of childhood that to cover the subject fully would entail a systematic review of practically the entire field of pediatrics. In the space allotted, a presentation of this nature would, necessarily, deteriorate into a cursory and superficial resumé of recent medical publications with no attempt at critical appraisal. In this article I propose rather to follow a more selective course.

A number of fundamental investigations have been reported in recent years which promise to be of outstanding significance in the future development of medical progress. Amongst these must be included the work of Stanley on the essential nature of filterable viruses, the biochemical investigations of Urey on heavy isotopes and their use in the elucidation of physiologic problems by Schoenheimer and his coworkers, the identification of the chemical structure of various vitamins and hormones by a number of workers and, in the use of sulfanilamide, the renewed demonstration by Domagk of the value of chemotherapy. The objectives dictating the choice of subjects discussed here will however be those of present practicability and usefulness.

In recent years the pediatrician has been presented with numerous methods of diagnosis, prophylaxis and treatment. Before accepting a new procedure for general use, the results of clinical trial under controlled conditions should be critically examined. Discrimination is needed to avoid either excess haste or needless delay in utilizing experimental results in general practice. I shall undertake the admittedly hazardous task of attempting to evaluate the present state of our knowledge regarding some of these newer procedures, realizing full well that such a plan of presentation leaves one open to justifiable criticism since the choice of subjects may be considered inept and the assessments of

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value erroneous. Because of limitations of space, detailed evidence supporting evaluations will be omitted and I hope statements which may seem dogmatic will be condoned.

Infections of the Urinary Tract

The high incidence of infections of the urinary tract in childhood, their potentially serious consequences and the changing concepts of diagnosis and treatment make consideration of pyuria advisable. By the term pyuria is meant the persistent presence of clumps of pus and bacteria in uncentrifuged, "clean" or catheterized specimens of urine and not an occasional white blood cell in a casual specimen. Until recently pyuria as a complication of upper respiratory infections in children aroused little apprehension since the attending pediatrician was aware that the condition was as a rule self-limited, clearing after a shorter or longer period on a regimen of forced fluids and the administration of alkalies or drugs such as methenamine and acid phosphate. A series of recent discoveries have continuously modified the treatment of this acute condition.

Following the demonstration by Helmholz that high fat, low carbohydrate diets accelerated recovery by leading to the excretion of an acid urine with a high concentration of beta-hydroxybutyric acid which was bactericidal, this form of therapy was frequently used. It never became popular however because of the difficulty of persuading children to take these unpalatable diets.

Shortly thereafter Rosenheim found that the results obtained with the ketogenic diet could be duplicated more easily by the administration of mandelic acid. This aromatic acid is neither conjugated nor oxidized in the body but is excreted unchanged, imparting a high degree of acidity to the urine. To facilitate this, the ammonium salt—which is less irritating than the free acid—is administered and if the desired acidity is not secured by the use of ammonium mandelate alone, ammonium chloride or acid sodium phosphate may be used.

The following technique for mandelic acid therapy is recommended: Elixir of ammonium mandelate (a 25 per cent solution) is given by mouth in dosages of from 1 to 3 drams four times daily, after meals. This dosage supplies from 4 to 12 grams of mandelic acid daily. Infants under one year receive 4 grams daily; children over ten years, 12 grams; and children of intermediate ages, intermediate amounts. This level of

dosage yields mandelic acid concentrations of 0.5 per cent or higher in the urine. Therapy is continued for a period of two weeks even though pyuria disappears earlier. During this time, the children are placed on an acid-ash diet and the fluid intake is adjusted to meet the fluid requirements. Urine specimens are examined at least once daily for sediment and acidity. Optimal acidity is represented by a pH of less than 5.5 as determined by the indicator, chlorphenol red, which turns from a pink to a yellow color at this reaction. If the desired acidity is not obtained after a day or two by the use of the salt alone, solution of ammonium chloride in daily dosages of from 2 to 8 cc. is added to the regimen. If bacteriuria or pyuria persists despite the two weeks of therapy, a rest period of one week is followed by a second course. If no results are obtained, continuance of this form of treatment is usually of little or no value.

At this point, a word of caution should be sounded. Mandelic acid therapy should not be employed in the presence of impaired renal function, large numbers of red blood cells in the urine or fever. When the pyuria results from infection by urea-splitting organisms such as B. pyocyaneus, aerobacter and proteus, the ammonium salts of mandelate or the accessory acidifier should be replaced by sodium salts.

Mandelic acid therapy has demonstrated its value in acute pyurias unassociated with congenital anomalies of the urinary tract where the offending organisms have been the common gram negative bacilli such as B. coli or the less common cocci, particularly S. fecalis.

The advent and increasing popularity of sulfanilamide led inevitably to its use in the treatment of pyuria in children and it has proved a potent therapeutic agent in practically all forms of acute urinary tract infections. The advantage of this drug over mandelic acid is that it exerts a sterilizing action in urine, either alkaline or acid. Fluid restriction, an acid-ash diet and accessory acidifiers are therefore unnecessary when sulfanilamide is employed.

The technique of this form of therapy as used in the children's clinic of the New York Hospital follows:

Sulfanilamide tablets are administered orally in a total daily dosage of 0.2 grams per kilogram of body weight, divided into four equal parts and given at six hour intervals. This dosage exceeds that recommended by Helmholz but we have found the larger amounts more effective clinically and only with the larger dosage have blood concentrations of

sulfanilamide been obtained within the accepted optimal range of 10 mg. or more per 100 cc. of blood.

This therapy is continued for two weeks followed by a rest period of one week. A second course is instituted when necessary. Sulfanilamide should not be used in dehydrated or debilitated states, in the presence of severe anemia, leukopenia or nephritis. Therapy should be discontinued with the appearance of severe cyanosis, jaundice, sulphemoglobinemia or methemoglobinemia, hyperpyrexia, anemia or granulocytopenia. Morbilliform eruptions occur not infrequently but are of lesser import. With cessation of therapy and the forcing of fluids the above manifestations almost invariably subside. Saline purgatives should be avoided during therapy.

The conclusions expressed regarding the status of mandelic acid therapy also apply to sulfanilamide therapy. In the absence of congenital anomalies of the urinary tract or when the offending organism is not S. fecalis–a normal inhabitant of the intestinal tract–the pyuria and bacteriuria clear up in the majority of instances during the first two weeks of treatment.

Despite the proved efficacy of these newer forms of therapy, the pediatrician not infrequently encounters infants and children in whom the pyuria is resistant to all forms of medical treatment or may recur after temporary subsidence. In these patients irreparable harm may result from improper treatment. In our experience as well as in the far greater experience of Meredith Campbell and others, the persistent pyuria in a vast majority of these young patients is associated with a congenital anomaly of the urinary tract with consequent urinary stasis and secondary infection. Since many of these anomalies are amenable to surgical intervention a complete urologic study is obviously desirable, including intravenous urography, cystoscopy and retrograde pyelography where indicated. Disastrous crippling of renal function and atrophy of kidney parenchyma due to neglect of this condition are still all too common. There is no justification for following a so-called conservative course in a young child whose pyuria has resisted adequate medical treatment for longer than four, or at most six, weeks. Such youngsters should have the benefit of urologic consultation.

Pertussis

None of the newer prophylactic measures has attracted more atten-

tion than the vaccines against whooping cough. The importance of this disease as a cause of death in infants is good reason for this attention. The yearly case rate in the United States is approximately 300,000 with 5,000 deaths, and the mortality rate of infants under two years is about 15 per cent of those affected. The difficulty of early diagnosis, and therefore of isolation during the highly contagious catarrhal stage of the disease, makes it probable that eventual eradication of pertussis will depend on the widespread use of preventive immunization.

Since the re-introduction by Sauer in 1926 of the use of vaccines for protection against whooping cough, the method has been widely publicized. Sauer's special contributions are the method of preparation of the vaccine and the higher dosage recommended. Hemolytic strains from freshly isolated cultures are grown on a solid medium containing human blood and the culture is carefully harvested with a minimum of washing in the preparation of the vaccine. The dosage advocated is 1.0, 1.5 and 1.5 cc. injected intramuscularly in each buttock at weekly intervals, making a total of 8 cc. or 80 billion killed organisms, given preferably between the ages of seven to ten months. In children over three years the latter two doses may be increasd to 2 cc. so that the total dose is 10 cc. Development of immunity, according to Sauer, requires from three to four months and its duration supposedly extends for from one to five years, according to different observers.

A number of other vaccines have been proposed for active immunization. These include the "undenatured" bacterial antigen of Krueger in which the organisms are killed by mechanical disruption rather than by chemical agents; the vaccine of Mishulow of the Department of Health of New York City in which the antigen consists of both organisms and toxic filtrate; mixed vaccines containing not only Bordet-Gengou bacilli but also streptococci and staphylococci; and finally a bacteria free filtrate detoxified with formalin. Most of the latter products are advocated for immunization in patients already exposed and the dosage recommended varies from 0.5 to 2 cc. every day or every other day for two to six injections.

Conclusions regarding the efficacy of present day vaccines are still equivocal. Available statistical evidence is predominantly favorable, but the results which may be obtained in any given case are not predictable. Failures to immunize undoubtedly occur in many instances and many questions remain unanswered. If immunity develops, how long does

it last and how variable is it? What role does the frequently poor immunologic response of infants to injections of antigen play in explaining the failures which occur in this age period? Is the dosage at present in use optimal? It is known that humoral phenomena such as agglutinin response and complement fixation which result from injections with any vaccine afford criteria for tissue immunity which are not necessarily reliable.

In our present state of knowledge, the conservative attitude toward these measures may be summarized as follows: The vaccines at present available merit continuation of experimental studies under controlled conditions but cannot as yet be recommended as a general public measure analogous to the accepted use of specific prophylaxis against smallpox and diphtheria. Since there is little indication that injections of pertussis vaccine are harmful, their use in younger children of large families, nurseries, and institutions where intimate exposure cannot be avoided and in older debilitated or tuberculous children may be countenanced since it offers hope of at least partial protection.

It is my belief that convalescent human serum injected in dosages of 10 to 20 cc. intramuscularly in infants and older sick children during the incubation period of pertussis may reduce the severity of ensuing symptoms. A considerably higher number of observations are however necessary to validate this opinion.

Poliomyelitis

Another infectious disease of considerable public concern is anterior poliomyelitis. Recent advances in knowledge of virus diseases in general and of this disease in particular have not as yet led to the discovery of successful prophylactic measures.

Early reports of successful protection against poliomyelitis by subcutaneous injections of either attenuated or inactivated virus have in the main not been substantiated. That these methods are not free from danger is shown by reports of the development of the disease in a number of children who were inoculated six to fourteen days prior to the onset of symptoms. Both Rivers and Flexner believe that in the present state of our knowledge, attempts to induce active immunization against poliomyelitis by injections of virus are unsound. "No methods have as yet been devised which can so modify the virus that it will retain its immunizing power or is merely reduced in potency so that it immunizes

in some instances and paralyzes in others."

Approximately 150 inoculations with an "inactivated" virus were given in our clinic in 1936 without the development of poliomyelitis in any of our cases, but in view of the evidence cited this procedure should be discouraged. Within the last month, Stanley and his coworkers have demonstrated that x-radiation of certain viruses results in destruction of their pathogenicity with retention of their antigenicity. This offers much promise for the future.

Because of the unsuccessful attempts to immunize actively against poliomyelitis by injections of virus, Armstrong and Harris used intranasal sprays of picric acid, zinc sulphate and other chemicals and protected monkeys against infection by the intranasal route. Although the animal work is fairly conclusive, it has not been confirmed for humans in its first field trial. During the recent epidemic in Toronto, reported by Brown, Tisdall and others, 4713 children were sprayed nasally with 1 cc. of a mixture of zinc sulphate (1 per cent), pantocain (1 per cent) and sodium chloride (0.5 per cent) on two occasions at ten to twelve day intervals. Twenty-five per cent of the children developed anosmia, indicating that the spray in this group had reached the olfactory nerve endings. Eleven subsequently developed poliomyelitis compared with an identical case rate of eighteen in 6300 control children.

Convalescent human serum as a means of passive prophylaxis and treatment has not been encouraging. The presence of humoral antiviral substances does not parallel tissue immunity, for monkeys have contracted the experimental disease even though their serum had neutralizing antibodies at the time of intracerebral inoculation of the virus.

To date, none of the recommended prophylactic procedures against poliomyelitis has demonstrated the combination of practicability, safety and effectiveness necessary for adoption as a public health measure, but the intensive studies currently being carried out presage valuable contributions in the near future.

Vitamins

Outstanding advances have recently been made in our knowledge of the biochemistry, physiology and clinical use of vitamins. A number of accessory food factors necessary for proper nutrition in infancy and in childhood have been obtained in pure form and their chemical structure identified. In many instances they have been synthesized and made

available for therapeusis. Earlier recognition of subclinical deficiency states may soon be possible for a number of vitamins because the physiologic functions subserved by these vitamins are being more accurately defined and simple chemical tests for assaying body reserves are being developed. Standardization of vitamins in terms of international or chemical units is replacing the tedious and uncertain technique of biologic assay in animals. The present discussion will be limited to clinical aspects of the subject.

Vitamin A: Identification of the visual purple of the retina as a chemical sterol closely resembling vitamin A in chemical structure underlies the introduction of the biophotometer for detecting night blindness, a manifestation of vitamin A deficiency. Evidence collected throughout the country suggests that a surprisingly large number of both children and adults ingest inadequate amounts of this vitamin.

Wolbach has shown that lack of vitamin A is associated with widespread cornification and keratinization of mucosal epithelium in both animals and man and predisposes to infections. Because of this, there has been a growing tendency fostered by commercial concerns to assume that the resistance of children to infection may be augmented by increasing their intake of vitamin A. There is no evidence as yet that augmentation above accepted adequate levels of intake necessarily promotes the health and well-being of children. In our present state of knowledge, daily intakes of from 4,000 to 6,000 international units of vitamin A either in the diet, in the form of the provitamin, carotene, or as fish liver oil are presumably adequate to cover the needs of the growing child. In the presence of gastrointestinal disorders or chronic infections, larger intakes may be desirable.

Vitamin B: The vitamin B complex has been divided into at least six component fractions and the chemical structures of three have already been identified: B_1 as thiamin; B_2 as ribo or lactoflavin; and the P. P. or pellagra-preventing factor as nicotinic acid. It is too early to delimit the precise role of each of these components in human health and nutrition. Reliable biochemical methods are not yet available for assaying the body reserves of any of the constituents of the B complex, criteria of early obvious deficiency states are still largely guesswork, and accurate information regarding levels of optimal intake is still lacking. The use by pediatricians of the vitamin B complex in a variety of ailments is easily understandable but more extensive, carefully controlled clinical studies

are necessary to prove the value of these therapeutic agents in human beings. Present knowledge indicates that a diet containing from 300 to 400 international units of vitamin B_1 and 600 Sherman units of B_2 adequately cover the requirements of growing children. Authentic data are not yet available regarding the other components of the vitamin B complex.

Vitamin C: The identification of vitamin C as cevitamic acid (a glycuronic acid), its storage in the adrenal cortex and other tissues, the use of colorimetric tests of the blood and urine for estimating the body reserves are well established. That subclinical deficiency states occur, without the definite manifestations of scurvy, has been demonstrated by the use of tolerance tests in which the cevitamic acid content of the urine is determined following the ingestion of a test dose of the vitamin. Although deficiency of this vitamin has been implicated in a variety of diseases including acute rheumatic fever, poliomyelitis, diphtheria, upper respiratory infections, pertussis and symptomatic purpura; the causal relationship of lack of vitamin C has been generally accepted only in scurvy and dental caries. It should be mentioned that two other factors, designated "K" and "P", have recently been isolated from citrus fruits. These factors are apparently concerned with the coagulation of blood and with capillary permeability and appear to be separate and distinct from cevitamic acid itself.

The best available evidence indicates that the daily ingestion of from 150 to 300 international units or 10 to 20 mg. of crystalline cevitamic acid, equivalent in vitamin content to from 30 to 45 cc. of fresh orange juice, usually suffices to prevent the development of latent scurvy in infants and children. Amounts as great as 300 to 500 mg. of crystalline vitamin C have been administered orally and intravenously in the treatment of manifest scurvy without harmful effects.

Vitamin D: Recent investigations of the fat soluble, anti-rachitic vitamin D have advanced our methods for insuring its universal consumption by growing infants and children. During the past decade Windhaus and Alfred Hess discovered the identity of vitamin D and irradiated ergosterol and Hess and Steenbock demonstrated that ultra-violet irradiation rendered a large variety of foodstuffs antirachitogenic. As a result commercial concerns raced to irradiate all of their saleable products: milk, cereals, peanut butter, bread, cocoa malt, cigarettes and even underwear, in this "era of irradiation."

Coincidentally it was discovered that the liver oils of fish other than the traditional and time-honored cod contained in many instances higher concentrations of both vitamins A and D, and a variety of such concentrates became available for distribution. Finally, the synthesis of crystalline vitamin D, calciferol in England and drisdol in this country, provided another product for human consumption.

Evidence is accumulating that there may be more than one form of vitamin D and that products of different origin may have different antirachitic potencies in equivalent unitage. A daily intake of from 200 to 400 international units of vitamin D—the larger dosage being required for plant products—may be considered sufficient to prevent severe rickets, infantile tetany and subsequent development of severe dental caries. The relation of other clinical disorders to vitamin D deficiency has not as yet been unequivocally established.

Cryptorchidism

The interest of pediatricians in the newer knowledge of the endocrine glands is understandable since it is the function of the pediatrician to promote optimal growth and development. Pure extracts of many hormones are now available but the ease with which they may be obtained does not justify their indiscriminate use. Of these newer products a number have already demonstrated clinical value and from these will be selected for discussion the hormone treatment of cryptorchidism and of gonorrheal vulvovaginitis.

Only in the human does normal descent of the testes into the scrotum occur during fetal life. Since the blood of the human maternal organism and of no other species contains the anterior pituitary gonadotropic hormone in high concentrations throughout pregnancy, it has rightfully been assumed that the descent of the testes during the seventh to the eighth month of human fetal life is due to the action of this hormone. This assumption was verified by Engle who was able to induce premature descent of the testes in ten immature monkeys by the administration of extracts of pregnancy urine and of water soluble extracts of anterior pituitary. Since then the use of the anterior-pituitary-like (A. P. L.) principle of pregnancy urine for cryptorchidism has become increasingly popular. A reasonable attitude toward hormone therapy for cryptorchidism in our present state of knowledge might be stated as follows:

Lack of descent of the testes may be due to mechanical interference

with downward movement or inadequate stimulation by the gonadotropic hormone of the anterior pituitary. Since there are no conclusive means at present of differentiating between the two types (although certain associated signs such as body build, obesity, size of external genitalia, may lead one to suspect one or the other motivating factor in a given patient), a clinical trial with hormone therapy is indicated prior to surgical intervention.

In those patients in whom endocrine treatment fails to cause testicular descent, it frequently enlarges the genital structures, facilitating subsequent operative procedures. Proper regulation of dosage permits this beneficial result without risking premature puberty.

The optimal age for administration and the dosage of pregnancy urine extracts are still moot questions. The following procedure may be recommended:

Except in cases of associated large hernias requiring earlier repair, hormone therapy is always delayed until after the fifth or sixth year since the evidence in general indicates that the human undescended testis undergoes no degenerative changes prior to this age and because spontaneous descent may occur up to and beyond this age. At any time after this age, provided the patient has a true and not a pseudocryptorchid, 50, 100 and 200 rat units of pregnancy urine extract may be given subcutaneously during the first week. If no local or general reactions occur, 200 rat units are given three or five times weekly for four to six weeks until a total of about 5000 units has been administered. In those patients in whom treatment is successful, the testes descend and enlarge, the scrotum becomes redundant and the penis enlarges.

Following cessation of treatment, the testicles may remain in the scrotum, or, as frequently happens, the size of the genitalia may regress and the testes recede into the inguinal canals. One may be reasonably certain when these results are obtained with endocrine treatment, that spontaneous descent will take place at puberty under the stimulus of the patient's own augmented secretion of gonadotropic hormone of the pituitary. To expedite this a second similar course of therapy may be given during the prepubertal period between eleven and thirteen years.

In our experience, increased dosage over more prolonged periods has failed to transform an unsuccessful into a successful result and, since premature puberty is possible with larger dosage, we abstain from its use. Two types of results have been observed in the unsuccessful cases

following the course of treatment prescribed above: first, patients in whom enlargement of the genitalia was produced without testicular descent; and second, cases, far fewer in number, in whom neither descent of the testes nor enlargement of the genitalia followed hormone therapy. In the first group it seems reasonable to assume that the penile enlargement indicates that at least one testis is present and capable of responding to adequate pituitary stimulation and that testicular descent is prevented by mechanical obstruction. These patients require operative intervention accompanied preferably by a course of hormone therapy before and possibly after operation. In the second group, complete failure following adequate dosage of gonadotropic hormone suggests either absence or atrophy of both testes, and that surgical treatment is also likely to fail. Such patients should be given androsterone or male sex hormone, although accurate knowledge concerning the ultimate results of such therapy will be obtained only with time.

Vaginitis

The popularity of hormone therapy for gonorrheal vulvovaginitis is ample evidence of the generally unsatisfactory results obtained with other forms of treatment. According to the annual report for 1937 of a committee of the Social Hygiene Association, twenty of twenty-four special vaginitis clinics in New York City used estrogenic substance either exclusively or as an adjuvant to other forms of therapy. Treatment with the follicular hormone of the ovary, either from pregnancy urine or ovarian extracts, was introduced by Lewis for infantile vaginitis on the assumption that cornification of the vaginal mucosa by estrogenic hormone would render it less susceptible to the gonococcus. This supposition was confirmed by the successful results obtained in the first small series of infants so treated.

Since then, many observers have demonstrated its general, although not universal efficacy. The present aim of hormone therapy is to administer a dosage adequate to produce cytological changes in the vaginal mucosa and a lowering of the vaginal pH to 5.5 or less—changes which were not obtained constantly with the earlier smaller dosage used. It may be stated definitely however that such changes are not invariably accompanied by cure of the gonorrheal infection.

More than 150 infants and children have been treated with hormone by Dr. Dooley in the vaginitis clinic of the New York Hospital. The

present method is as follows: Daily subcutaneous injections of from 2000 to as much as 10,000 I. U. of follicular hormone (in oil) are administered in increasing dosage until the desired change in cytology and acidity is obtained. The findings are checked weekly and often more frequently by vaginal smears and nitrazene paper tests for pH. The desired changes are usually obtained in from one to four weeks and sometimes earlier. Although the vaginal discharge and the number of gonococci tend to be reduced by this treatment, complete cure in twenty or thirty days, as frequently reported, has been the exception rather than the rule in our experience.

These less favorable results may be explained by the more stringent criteria for cure. No child is considered cured unless all vaginal discharge has ceased, vaginoscopic examination shows a normal cervix, and three negative cultures as well as smears have been obtained.

The complement fixation test is also used as a diagnostic and prognostic aid. A high titre in the blood indicates, in our opinion, a gonorrheal etiology of the discharge even though no organisms are present in the smear, and maintenance of the high titre affords evidence that the infection persists and that symptoms may recur.

The recent experience of Lewis suggests that local application of this hormone by daily vaginal instillation or suppositories is probably more effective than parenteral administration. In a relatively small number of patients in our clinic, the use of daily vaginal estrogenic suppositories or capsules in dosages of 1000 I. U. has seemed to accelerate recovery, but far greater experience with this modification is necessary under the same carefully controlled conditions before universal acceptance. No harmful by-effects such as hypertrophy of the breasts or precocious menstruation have been observed in our patients.

The apparently favorable reports with sulfanilamide in gonorrheal infections offer promising implications for the treatment of vulvovaginitis but an adequate number of observations on its value in the latter are not yet available.

Estrogenic therapy of gonorrheal vulvovaginitis in infants and children represents a definite therapeutic advance, since the results are in general more satisfactory than those obtained with the local instillation of antiseptic solutions or the injections of vaccine. The reservation must be made however that the generally unsuccessful results with vaccines may be due to inadequate dosage.

Apple Diet in Diarrhea

The apple diet in the treatment of diarrhea in infants and children merits mention because of its established value, its simplicity and its interesting historical background. Its use had a humble origin, analogous to that of smallpox vaccine, for German housewives had recognized its value long before Heister, in 1928, and Moro, in 1929, called attention to its efficacy.

Moro relates that in a prison camp during the World War epidemics of dysentery were common amongst the half starved prisoners, but that a number of them, surreptitiously ingesting forbidden fruit from several apple trees showed striking improvement in their symptoms. The camp physician used apples thereafter and reported marked success.

During the past five years favorable reports have appeared in the American literature and modifications have been introduced in an attempt to enhance the efficacy of raw apple. Apple powder, pectin-agar, cellulose, banana powder and honey have been suggested but their advantages are not yet established.

The physiological basis for the beneficial action of apple pulp in the gastrointestinal tract is not yet understood but the evidence suggests that the colloid pectin adsorbs and removes toxic substances. Organic acids, particularly malic, may supplement this colloid action by a sedative and astringent action which reduces peristalsis.

We have employed the raw apple diet in a small number of patients at the New York Hospital with promising results. The pulp of ripe apple, without the core or skin, was fed in varying amounts depending upon the infant's willingness to ingest it. An effort was made to give at least two to four tablespoonfuls every two hours for two days, supplemented by water or weak tea. On this régime, the stools assumed the character of practically pure apple within twelve to twenty-four hours and usually remained formed after boiled skimmed or protein milk was substituted in small amounts for the water at the end of forty-eight hours.

Encouraging results were obtained in both bacillary dysentery and other forms of diarrhea in older infants and children. Frequent refusal in infants under five to six months and an irritative stomatitis in infants under two months made the apple diet less practicable in this age group, but this form of treatment can be of great service to the pediatrician because its simplicity may obviate hospitalization.

In closing, I should like to point out that present progress in the study of viruses, of the biochemistry of vitamins, and of endocrinology, and in the psychiatric rapprochement with pediatrics, are harbingers of the clinical progress which may be expected in the next decades. These fundamental contributions should lead us to aspire to even higher standards for mental, emotional and physical growth and development of children.

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PROCEEDINGS OF ACADEMY MEETINGS

STATED MEETINGS

OCTOBER 6—***The New York Academy of Medicine.*** Executive Session—Reading of the minutes. ¶ Papers of the evening; Symposium on evaluation of sulfanilamide therapy—a] Fundamental problems of chemistry and pharmacology—mechanism of the action, E. K. Marshall, Jr., (by invitation), Professor of Pharmacology and Exerimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore; b] Clinical aspects, Reuben Ottenberg, Assistant Clinical Professor of Medicine, College of Physicians and Surgeons, Columbia University; Discussion by Emanuel Appelbaum, Homer F. Swift, William E. Studdiford, Francis G. Blake. ¶ Report on election of members.

OCTOBER 20—*The Harvey Society (in affiliation with The New York Academy of Medicine).* The first Harvey Lecture, Some Aspects of the Intermediary Metabolism of the Steroid Hormones, Guy F. Marrian, Professor of Biochemistry, The University of Toronto.

SECTION MEETINGS

OCTOBER 4—*Dermatology and Syphilology.* Presentation of cases, Miscellaneous from—a] Clinics; b] Hospitals; c] Members. ¶ General discussion. ¶ Executive session.

OCTOBER 7—*Surgery.* Reading of the Minutes. ¶ Presentation of cases—a] 1. Advanced recurrent carcinoma of the lip treated by radical excision and plastic repair; 2. Advanced recurrent basal cell carcinoma of the nose treated by radical excision and plastic reconstruction by three pedicled flaps from cheeks and forehead, William J. Hoffman, Discussion by Herbert Willy Meyer; b] Two cases of perforated marginal ulcer (gastro-jejunal), James E. Thompson, Discussion by Condict W. Cutler, Jr.; c] Fibro-sarcoma of forearm with amputation, Louis René Kaufman, Discussion by Morris K. Smith. ¶ Papers of the evening—a] Cervical nodes in intraoral carcinoma; an objective method of determining operability, James J. Duffy; Discussion by William F. MacFee; b] Interscapulo-thoracic amputation for malignant tumors of the upper extremity, Bradley L. Coley, George T. Pack, Gordon McNeer (by invitation); Discussion by Norman L. Higinbotham.

OCTOBER 11—*Neurology and Psychiatry.* Reading of the minutes. ¶ Papers of the evening—a] Transitory neurologic changes during hyperthermia, Ralph T. Collins (by invitation); Discussion by Israel Wechsler, William Snow, Richard Brickner; b] "Cachexia" nervosa—a psychoneurotic Simmond's syndrome, Irving H. Pardee; Discussion by Clarence P. Oberndorf, Robert Loeb; c] The problem of marihuana in psychiatry, Walter Bromberg (by invitation); Discussion by Hon. Frederick L. Hakenburg (by invitation), Alexander Gettler (by invitation), Eugen Kahn (by invitation).

OCTOBER 13—*Pediatrics.* Reading of the minutes. ¶ Papers of the evening—Symposium on x-ray diagnosis of bone lesions in infancy and childhood. Presented by the Department of Radiology of the New York Hospital, John R. Carty, Director.

OCTOBER 17—*Ophthalmology.* The regular meeting was postponed.

OCTOBER 18—*Medicine.* Reading of the minutes. ¶ Papers of the evening—a] Unusual clinical types of coronary artery disease, William D. Stroud, Philadelphia (by invitation); Discussion by Lewis A. Conner; b] Changes in the form of the electrocardiogram caused by induced anoxemia: A clinical test for coronary insufficiency, Robert L. Levy; Discussion by Harold J. Stewart; c] Drug therapy in coronary artery disease, Harry Gold; Discussion by Cary Eggleston.

OCTOBER 18—*Dermatology and Syphilology.* Presentation of Cases—Miscellaneous from—a] Clinics; b] Hospitals; c] Members. ¶ General discussion.

OCTOBER 21—*Orthopedic Surgery.* Reading of the minutes. ¶ Presentation of cases—Xanthoma of the knee, Donald E. McKenna. ¶ Papers of the evening—a] Management of pathological fractures, Edgar A. Bick; Discussion by Philip Wilson and Samuel Kleinberg; b] Planigraphy in orthopedic surgery, Maurice M. Pomeranz, Henry K. Taylor. ¶ General discussion.

AFFILIATED SOCIETIES

OCTOBER 17—*The New York Roentgen Society.* Presentation of cases was omitted. ¶ Papers of the evening—a] The experimental and pathological aspect of leukemia, lymphosarcoma and Hodgkin's

disease, Maurice N. Richter (by invitation); b] Indication for surgery, A. P. Stout (by invitation); c] Roentgenotherapy in leukemia, Albert Kean, Nathan Rosenthal (by invitation); d] Roentgenotherapy of lymphosarcoma and Hodgkin's disease, Maurice Lenz. ¶ Discussion opened by Lloyd F. Craver (by invitation), Kenneth R. McAlpin (by invitation), Ross Golden.

FRIDAY AFTERNOON LECTURES

TO BE HELD AT 4:30 O'CLOCK

1938 - 1939

December 2
The influence of emotional factors upon physiological and pathological processes
FRANK FREMONT-SMITH

December 9
"Sciatic" pain, its differential diagnosis and treatment
ALAN DEFOREST SMITH

December 16
The management of the emergencies in patients with heart disease
CLARENCE E. DE LA CHAPELLE

January 6
Diagnosis and treatment of some diseases of the newborn infant
HOWARD REID CRAIG

January 13
Functional digestive disturbances
WALTER C. ALVAREZ, Minnesota

January 20
Bulkley Lecture: Recent additions to our knowledge of the treatment of breast cancer
FRANK E. ADAIR

January 27
The toxemias of pregnancy
ARTHUR M. FISHBERG

February 3
Laboratory aids and their clinical value
WILLIAM S. TILLET

February 10
The use of newer preparations of insulin in the treatment of diabetes
WALTER R. CAMPBELL, Toronto

February 17
The newer methods of treatment of schizophrenia
KARL M. BOWMAN

February 24
Present day treatment of non-tuberculous urinary infections
MEREDITH F. CAMPBELL

March 3
Migraine headache—its mechanism and treatment
HAROLD G. WOLFF

March 10
The problems presented by infections of the nasal accessory sinuses, and their management
SAMUEL J. KOPETZKY

March 24
The recognition of obscure fevers
GEORGE BLUMER, New Haven

March 31
The management of obesity
FRANK G. PETTENGIL

April 7
The endocrinological basis for gynecological organotherapy
EMIL NOVAK, Baltimore

April 14
Hemorrhagic states—recent clinical and therapeutic developments
PAUL REZNIKOFF

April 21
Chronic non-tuberculous pulmonary infections
LOUIS HAMMAN, Baltimore

April 28
Status hypoplasticus: its bearing on all fields of medicine and a discussion of the automatic compensatory mechanisms involved
WALTER TIMME

PROGRAM OF STATED MEETINGS

1938 - 1939

December 1, 1938

Serum therapy in pneumonia

1. Present status of serum therapy, Russell L. Cecil
2. Results with rabbit serum, Colin M. MacLeod
3. Program for meeting the pneumonia situation, Wheelan D. Sutliff

Discussion: Edward Tolstoi
Jesse G. M. Bullowa
Ralph S. Muckenfuss

January 5, 1939 — ANNUAL MEETING

Chronic gastritis

1. Recent advances in diagnosis by gastroscopy, Rudolf Schindler
2. Clinical aspects, Burrill B. Crohn

February 2, 1939

Vitamins with special reference to therapy

1. Vitamin A, Arthur M. Yudkin, New Haven
2. Vitamin B, Norman Jolliffe
3. Vitamin C, Gilbert Dalldorf, Valhalla

Discussion: Arthur J. Patek, Jr.
Soma Weiss, Boston
Philip Finkle

March 2, 1939

Symposium on arthritis

1. Gout, Philip S. Hench, Rochester, Minnesota
2. The nature of hypertrophic arthritis (degenerative joint disease), Walter Bauer, Boston
3. Evaluation of newer methods of therapy, Ralph Boots

Discussion: Philip D. Wilson
Edward F. Hartung
Albert B. Ferguson

May 4, 1939

Recent advances in the treatment of peripheral vascular disease

1. Clinical manifestations, Irving S. Wright
2. Medical treatment, Edgar V. Allen, Rochester, Minnesota
3. Surgical treatment, Reginald H. Smithwick, Boston

Discussion: Beverly Chew Smith
James C. White, Boston

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